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DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

Juvenile Diabetes Research

Witness appearing before the
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DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Statement of the Director

National Institute of Diabetes and Digestive and Kidney Diseases

Chairman Levin, Senator Collins, and Members of the Subcommittee: As Director of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), I appreciate the opportunity to testify at this hearing on childhood diabetes, which is being held in conjunction with the "Children's Congress" of the Juvenile Diabetes Research Foundation International (JDRF). I know that the Subcommittee will be hearing important testimony today directly from children whose lives are affected by diabetes. On behalf of the NIDDK and the other institutes and centers of the National Institutes of Health (NIH), I am pleased to report to this Subcommittee and to the children and parents in the room today that we have a vigorous research agenda to conquer diabetes and its complications. We are increasing our knowledge of the disease. We are well on our way to developing more effective treatment and prevention strategies. We are working diligently toward a true cure.

One of the most important health care issues facing our Nation is the increasing burden of diabetes. According to the Centers for Disease Control and Prevention (CDC), diabetes affects an estimated 16 million Americans, including both genders, the young and the old, all races and ethnic groups, the rich and the poor. Consistent with the topic of today's hearing, I will focus my testimony on diabetes in children, who, in many ways,

suffer most from the disease. They have the disease from an early age and must endure lifelong treatment. They must carefully adjust what they eat and everything they do--from schoolwork to sports--in order to manage their disease. Even with a continuous struggle to follow such regimens, they may still develop serious, long-term complications of diabetes.

Approximately one million Americans have type 1 diabetes, which is typically diagnosed in childhood, adolescence or young adulthood. They must have daily insulin administration to survive, and must monitor their blood glucose levels throughout the day and night. While the value of maintaining blood glucose control in preventing or delaying the onset of complications has been demonstrated through NIH research, this therapy is extremely difficult and is not without risks.

We are also very concerned about reports that more and more children are being diagnosed with type 2 diabetes. While patients with type 2 diabetes usually do not lose all of their insulin-producing ability and thus may not require insulin administration, they are susceptible to the same complications as those with type 1 diabetes.

The NIH has established a broad consultative process to frame a productive diabetes research agenda for fiscal year (FY) 2001 and beyond. Critical to this process is the scientific advice NIH has garnered from a variety of workshops and conferences, from the Strategic Plan of the congressionally established Diabetes Research Working Group, from our National Advisory Councils, and from the Juvenile Diabetes Research Foundation International (JDRF), with whom we have excellent interactions and complementary research programs. In addition to the growth in diabetes research through regularly appropriated funds, the NIH has effectively deployed the separate,

special funding stream for research on type 1 diabetes for the launch of major new initiatives. We are focusing our research agenda for type 1 diabetes around six important goals: to understand the genetics and epidemiology so that we can identify who is at risk for developing diabetes, to prevent or reverse the disease, to develop cell replacement therapy as a true cure for diabetes, to prevent or reduce hypoglycemia (low blood sugar) which limits tight control of blood sugar, to prevent or reduce complications, and to attract new research talent to the field.

Understanding the Genetics and Epidemiology of Type 1 Diabetes

Type 1 diabetes has strong genetic determinants; over the last few years, several genes have been linked to type 1 diabetes, and several chromosomal regions have been identified that harbor additional genes that confer susceptibility to type 1 diabetes. The NIDDK is launching major new research initiatives related to the genetics of type 1 diabetes, in conjunction with the National Institute of Allergy and Infectious Diseases (NIAID), the CDC, and the JDRF. We are forming an International Type 1 Diabetes Genetics Consortium to analyze genetic data from U.S., European and Australian family collections. These data have the potential to identify the additional genes that confer susceptibility to type 1 diabetes. A related research initiative will expand current efforts to establish a central repository of genetic data relevant to type 1 diabetes and provide an Internet-based information service for researchers through the International Histocompatibility Working Group.

We are also stepping up research to uncover the environmental “triggers” that, in combination with a genetic predisposition, may make some individuals especially prone

to developing the disease. In order to understand the interplay of genetic and environmental factors in type 1 diabetes more fully, the NIDDK is bolstering research on the epidemiology of the disease, in collaboration with the CDC, the NIAID, the National Institute of Child Health and Human Development (NICHD), and the National Institute of Environmental Health Sciences (NIEHS). One project will establish a large population of siblings, children, and parents of individuals with type 1 diabetes to identify genetic and environmental causes of the disease. By studying the interaction of genes, the environment, and the immune system, we may be able to identify factors that trigger the onset of autoimmunity in type 1 diabetes--the destructive process in which the body's immune defense system destroys its own insulin-producing cells. Given that type 1 diabetes may have its roots very early in life, another project will identify newborns genetically at risk for type 1 diabetes and follow them through the high-risk age (from 0 to 15 years) to identify additional genetic and environmental causes. Current research will be expanded at several sites, including Colorado, Florida and Washington. The CDC and NIDDK are also supporting a population-based registry to define the prevalence and incidence of diabetes in children. This project, entitled "SEARCH," will identify all children with diabetes in six regions of the country and will help us understand trends in disease development.

Genetic clues can also be derived from animal models, which are essential tools for understanding health and disease in humans. They help clarify the function of genes and provide systems for testing possible treatments that are not yet ready for human trials. Widely-used animal models of diabetes include the non-obese diabetic (NOD) mouse and the BB rat.

Reversing or Preventing Type 1 Diabetes

The foregoing genetic and epidemiologic studies should facilitate identification of those at high risk for development of type 1 diabetes. This identification, in turn, will allow us to intervene in an effort to prevent the disease. To spur the testing of promising new strategies to prevent or delay progression of type 1 diabetes, the NIDDK, in collaboration with the NIAID and NICHD, is creating a clinical trials network, the "Type 1 Diabetes TrialNet," a major recommendation of the Diabetes Research Working Group.

To develop a therapeutic or preventive vaccine, the NIH is actively pursuing research along several fronts. The NIDDK supports basic research to facilitate the establishment of a solid knowledge base enabling the selection, development and testing of promising candidate agents for the treatment and/or prevention of type 1 diabetes. Building on this knowledge base, the NIAID and NIDDK soon will be launching a program with the long-range objective of developing prevention strategies, including vaccines for autoimmune diseases, with emphasis on type 1 diabetes. This new research program is being co-sponsored by NICHD, the National Institute of Dental and Craniofacial Research (NIDCR), the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), the NIH Office of Research on Women's Health (ORWH), and the JDRF.

Developing Cell Replacement Therapy

Cell-based therapy offers the hope of a real cure for type 1 diabetes and would be far superior to the two current alternatives: daily insulin administration or whole pancreas

transplantation. Insulin administration via multiple daily injections or through an insulin pump is an extraordinarily difficult therapy and a poor substitute for the body's own finely tuned mechanism for releasing insulin only at the times and in the amounts necessary to maintain normal blood glucose levels. Whole pancreas transplantation is also problematic. It is major surgery, is usually done only in conjunction with a kidney transplant, and is not a feasible therapy for young children. In contrast to these current treatments, cell-based therapy would have many advantages for patients, including ease of administration--an important factor in the medical treatment of children.

Gaining knowledge about the genes of the insulin-producing beta cells of the pancreatic islets is also critical to combating type 1 diabetes. These cells are the key to insulin production and resulting glucose control. Thus, a new initiative will support the development of a gene expression array--a tool used to analyze which genes are turned "off and on" under different conditions, including diabetes. We expect that this research will provide important insights about possible new molecular targets for the treatment and prevention of type 1 diabetes.

Recent advances have sparked an exciting wave of new hope that a cure for type 1 diabetes can be realized through pancreatic islet transplantation. The crest of that wave is a promising study in Edmonton, Alberta, Canada, in which islet transplantation permitted a small number of people with type 1 diabetes to remain healthy for over a year without daily insulin injections. The NIH is now expanding clinical studies to exploit and extend these impressive findings. One major NIH effort, the Immune Tolerance Network (ITN), is a consortium of research institutions, led by the NIAID, which seeks

to replicate the successful results of the Edmonton protocol in a larger number of patients.

In complementary research, the NIDDK, in conjunction with the Department of the Navy, has established a Transplantation and Autoimmunity Branch, in which several islet transplants have been performed in adult patients with severe type 1 diabetes. The Walter Reed Army Medical Center and the University of Miami's Diabetes Research Institute are also collaborating in this research. The National Center for Research Resources (NCRR) also plans to establish up to six islet isolation centers across the U.S. to coordinate procurement of pancreatic tissue, isolation of islets, and their distribution for use in research protocols. These centers would also perform research and development to improve islet isolation techniques. In addition, the NIDDK will support an islet/beta cell transplant registry to collect data from all institutions performing islet and beta cell transplants in North America. As islet transplantation continues to be perfected, we will need to address two issues that could limit its widespread clinical application: (1) inadequate supplies of islets and (2) imperfect methods to prevent transplant rejection. We have several initiatives under way to resolve these issues.

First, we are accelerating research on many aspects of beta cell development and function so that we can increase supplies of donor pancreatic tissue for transplantation, possibly by developing alternative sources of islet beta cells. With NIDDK leadership, the NIH is taking a significant step in the development of cell-based therapy by establishing a new comprehensive beta cell project, as recommended by the Diabetes Research Working Group. The consortium approach will provide scientists with access to information, resources, technologies, expertise, and reagents that are beyond the means

of any single research effort. A comprehensive understanding of the molecular basis of beta cell development and function will then help to generate new research tools and to provide critical insights into the prevention and treatment of type 1 diabetes. Another approach to cell-based therapy is research on laboratory-generated replacement cells.

Second, we are supporting research on alternatives to the lifelong immunosuppressive drug treatments that are currently required to prevent rejection of transplanted islets and kidneys. One innovative research program, led by the NIAID and NIDDK, is developing methods to induce immune tolerance to transplanted kidneys and islets in non-human primates so that the grafts will be accepted by the recipient's immune system without the need for global immunosuppression. Because of the similarities between the human and non-human primate immune systems, results from this program will directly influence studies in the Immune Tolerance Network, TrialNet, and other NIH and JDRF supported clinical trials in islet and kidney transplantation. Such novel approaches to educating the immune system not only increase the likelihood of achieving a true cure for type 1 diabetes, but may also offer hope of preventing the disease in those at risk. Through these combined efforts, we are hopeful that islet transplantation can become the real cure we are all seeking for patients with type 1 diabetes, many of whom are children and young adults.

Reducing or Preventing Hypoglycemia in Type 1 Diabetes

The medical management of children with type 1 diabetes is particularly challenging. The occurrence of low blood sugar is a major factor limiting the ability to achieve good metabolic control and thus reduce the risk of complications. Very young

children cannot be taught the symptoms of low blood sugar or to alert their parents to take action when sugar levels drop dangerously low. Symptoms of severe low blood sugar can include seizures or loss of consciousness, which can be very frightening and may cause permanent problems. The NIDDK, in conjunction with the National Institute of Neurological Disorders and Stroke (NINDS), the National Institute of Nursing Research (NINR), NICHD and the JDRF, is expanding research to understand the pathways involved in being aware of hypoglycemia, and clinical research on methods to reduce or prevent hypoglycemia. In addition, NICHD and NIDDK are collaborating on a new initiative to encourage research on subcutaneously implanted glucose sensors in children with diabetes to monitor their blood sugar levels around the clock. Clearly, this advance would mean a substantial improvement in the quality of life for these children and their families, especially avoiding night-time hypoglycemia and elevated blood sugar levels immediately following meals.

Preventing or Reducing the Complications of Type 1 Diabetes

The complications of diabetes affect virtually every system of the body. Diabetes is the leading cause of kidney failure, new blindness in adults, and non-traumatic amputations. It is a major risk factor for heart disease, stroke, and birth defects; shortens average life expectancy by up to 15 years; and costs the nation in excess of $100 billion annually in health-related expenditures. The NIDDK, in collaboration with the National Eye Institute (NEI), NIDCR, NHLBI, and NINDS, is supporting numerous initiatives to reduce and prevent the complications of diabetes. We are increasing research efforts to identify new targets for therapy. We are encouraging the development of surrogate

markers for clinical trials by expanding the study of how genes function in tissues commonly involved in diabetes complications and by the development of improved diagnostic techniques. The NEI is initiating clinical trials relevant to diabetic eye disease. Several promising new drugs are under development to prevent diabetic eye disease and other complications involving the small blood vessels. We are also working to identify genes that may increase susceptibility for the development of the eye and kidney complications of diabetes.

Attracting New Talent to Research on Type 1 Diabetes

In order to accelerate the pace of research, a cadre of exceptionally talented and dedicated researchers is needed to bring the power of their intellects and expertise to bear on understanding, treating, preventing and curing type 1 diabetes. As the base of fundamental knowledge about type 1 diabetes grows, the opportunities also increase to translate this information into new diagnostic, preventive and therapeutic strategies. The NIDDK is supporting initiatives to foster the development of "bench to bedside" research through a partnership of both basic and clinical scientists in order to bring discoveries in the laboratory more rapidly to a clinical setting in which the patient can benefit. In addition, we are encouraging diabetes researchers to act as "talent scouts" to identify leading scientists with expertise or cutting-edge technology and bring them into type 1 diabetes research. New awards will support partnerships between such scientists and type 1 researchers.

I am grateful for the opportunity to share with you these examples of the many exciting NIH research efforts directed toward conquering diabetes in children. Diabetes places a tremendous burden on patients and their families, especially when it strikes in childhood. Through research, we will find the means of lifting the strain of this disease from their shoulders. Today, there is an unprecedented sense of enthusiasm and momentum in the diabetes community. We are eager to pursue the many scientific opportunities made possible by the biotechnology revolution. We are encouraged by the dedicated efforts of patients and their families, by organizations such as the Juvenile Diabetes Research Foundation International, and by the Diabetes Caucus. We are grateful for congressional interest and support, which have enabled us to undertake many of the research initiatives I have described to you. It is a privilege for me to be able to share the vigor and the promise of diabetes research with this Subcommittee, and with the children and parents affected by diabetes--who are always on our minds and in our hearts. I am pleased to answer any questions you may have.

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National Institutes of Health
National Institute of Diabetes and Digestive and Kidney Diseases

Biographical Sketch

NAME	Allen M. Spiegel, M.D.
POSITION	Director, National Institute of Diabetes and Digestive and Kidney Diseases
BIRTHPLACE	Germany
DATE	May 18, 1946
EDUCATION	B.A., Columbia College, 1967 M.D., Harvard Medical School, 1971
EXPERIENCE	
1999-present	Director, National Institute of Diabetes and Digestive and Kidney Diseases, NIH
1990-1999	Director, Division of Intramural Research, National Institute of Diabetes and Digestive and Kidney Diseases, NIH
1993-present	Chief, Metabolic Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases, NIH
1988-1993	Chief, Molecular Pathophysiology Branch, Metabolic Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases, NIH
1985-1988	Chief, Section on Molecular Pathophysiology, Metabolic Diseases Branch, National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases, NIH
1977-1984	Senior Investigator, Metabolic Diseases Branch, National Institute of Arthritis, Metabolism, and Digestive Diseases, NIH

1973-1976	Fellow, NIH Endocrinology Training Program, Clinical Associate, Metabolic Diseases Branch (Dr. G. D. Aurbach, Chief), National Institute of Arthritis, Metabolism, and Digestive Diseases, NIH
1971-1973	Intern and Assistant Resident in Medicine, Massachusetts General Hospital, (Dr. Alexander Leaf, Chief)

HONORS AND AWARDS

1966 - Elected to Phi Beta Kappa
1967 - B.A. Summa Cum Laude
1971 - Elected to Alpha Omega Alpha
1971 - M.D. Cum Laude
1988 - Outstanding Service Medal – U.S. Public Health Service
1990 - Meritorious Service Medal – U.S. Public Health Service
1990 - Jacobaeus Prize – Nordisk Insulin Foundation
1993 - Plenary Lecturer – Japan Endocrine Society
1993 - Aurbach Memorial Lecturer – American Society for Bone and Mineral Research
1994 – Harrison Memorial Lecturer – Endocrine Society of Australia
1996 - Komrower Memorial Lecturer – Society for the Study of Inborn Errors of Metabolism
1998 - Edwin B. Astwood Lecture Award – Endocrine Society (U.S.A.)

PROFESSIONAL ORGANIZATIONS

American Federation for Clinical Research
The Endocrine Society
American Society for Bone and Mineral Research
American Society for Clinical Investigation
American Society for Biochemistry and Molecular Biology
Association of American Physicians

LICENSURE AND CERTIFICATION:

Diplomate American Board of Internal Medicine, 1974
Board Certified in Endocrinology, 1975
Licensed in Medicine, Maryland